Chapter 7
Fatty Liver Disease

A1. Establish cohort study to prospectively analyze the natural history of the full spectrum of nonalcoholic fatty liver disease. The NIH-funded NASH Clinical Research Network has begun enrollment of both adults and children with all stages of NAFLD into a database and registry. A total cohort of 1,200 individuals will be enrolled at 8 sites and will be followed for 5 years, thereby providing resources for studies of natural history, genetics, metabolomics and biomarkers. (40%)

A2. Conduct phase I and II clinical trials of candidate therapies for NASH, TPN-associated liver disease, and alcoholic liver disease (e.g., silymarin, cytokines, anti-cytokines, anti-fibrotic agents). An RFA to create a Silymarin Clinical Research Consortium was published in 2005 (RFA-AT-05-006) and four clinical sites and a data coordinating center will be funded in 2006 to initiate phase I/II trials of silymarin in treating NASH and chronic hepatitis C. (0%)

A3. Develop more accurate animal models of nonalcoholic fatty liver disease (including secondary forms) and define molecular characteristics. Established animal models of alcoholic liver disease include a continuous intragastric (Tsukamoto-French) and a voluntary alcohol ingestion (Lieber-De Carli) model in rats, neither of which reliably produces substantial fibrosis. New models of NASH include genetically-altered mice with abnormalities in nuclear hormone receptors (PPARs, FXR, LXR), insulin and IGF signaling (IRS-1, IRS-2, IGF-I), satiety factors (ob, alpha MSH, melanocortin receptor, NPY), cytokines and their receptors (TNFα, TNFR1, IL6, IFNγ, TGFβ), and antioxidant factors (MAT-1α, NADPH oxidase). These animal models might also be used to assess whether alcohol further exacerbates the injury. A recent PA has encouraged applications in this area: "Animal Models of NIDDK-Relevant Diseases" (PA-05-049). (10%)

B1a. Elucidate the clinical, metabolic, proteomic, and gene expression patterns associated with various stages of nonalcoholic and alcoholic fatty liver disease. The NASH Clinical Research Network and several NIH-funded single center clinical groups are preparing cohorts for proteomic and gene expression studies. (10%)

B1b. Evaluate role and effects of bariatric surgery on NASH. Several cross-sectional studies have shown that 26 to 44 percent of persons have NASH and 2 to 5 percent have cirrhosis at the time of bariatric surgery. The Longitudinal Assessment of Bariatric Surgery (LABS) was funded as a cooperative agreement with a data coordinating center and 6 clinical sites and has initiated prospective studies of bariatric surgery, including studies of its effects on NASH. (10%)

B2a. Delineate the hepatic pathways of lipid metabolism and how they are altered in alcoholic and nonalcoholic liver disease. Stable isotope studies in humans suggest that, in NAFLD, there is increased hepatic lipogenesis and possibly reduced ability to mobilize hepatic lipids into VLDL. Further definition of fatty acid metabolic pathways in humans with fatty liver disease is needed and has been encouraged in the NIH PA on "Mechanisms of Alcoholic and Nonalcoholic Fatty Liver" (PA-05-119). (10%)

B2b. Develop noninvasive means of distinguishing steatosis from steatohepatitis and for grading and staging disease. Use of biomarkers and imaging studies including elastography are being evaluated in cohorts of patients with NAFLD, but clinically relevant markers are not available. Development of biomarkers in liver disease has been encouraged in the recent NIH PA on "Development of Disease Biomarkers" (PA-05-098). (0%)

B3a. Develop rapid-throughput systems to evaluate potential therapies of fatty liver disease. Until the metabolic abnormalities that underlie fatty liver disease are better defined, *in vitro* systems for screening small molecules will be limited. The NIH Roadmap for Medical Research encouraged research in this area through the RFA on "Pilot-Scale Libraries for High-Throughput Drug Screening" (RFA-RM-05-014), and a PA for similar grants was published as "Development of Assays for High-Throughput Drug Screening" (PA-05-068). (0%)

B3b. Develop therapy of acute alcoholic hepatitis that promotes recovery and decreases permanent injury. Small clinical trials of pentoxifylline and TNF antagonists showed modest promise, while a study of high dose TNF-α antibody and prednisone suggested that this approach may be harmful. Both pilot studies of innovative therapies and larger, more rigorous trials of promising therapies are needed. (0%)

C1a. Establish the efficacy and safety of therapy with insulin-sensitizing agents and vitamin E in NASH. The NASH Clinical Research Network recently began enrolling subjects into two prospective, randomized, placebo-controlled trials: one using pioglitazone in adults and another using metformin in children. Results should be available in two years. (20%)

C1b. Establish the efficacy and safety of therapy with SAMe in alcoholic liver disease. A pilot trial of SAMe therapy for alcoholic liver disease has been funded by the NIH. (0%)

C2a. Establish the prevalence and incidence of NASH in the general population as well as special populations in the United States, such as children, minority groups, and patients with diabetes and other dysmetabolic syndromes. The lack of noninvasive markers hampers efforts to determine the prevalence of NASH in the general population. Serum ALT elevations have been used as a surrogate marker for NAFLD and NASH, but the normal range is not clearly

defined (using age, sex, race and weight-based controls), and unexplained ALT elevations are not diagnostic of NAFLD. Imaging studies using NMR spectroscopy suggest that 31 percent of American adults have hepatic steatosis, with the rates being highest in Hispanics (45%), intermediate in whites (33%), and lowest in blacks (24%) (Browning JD, *Hepatology* 2004;40:1387). (20%)

C2b. Better define the safe amounts of alcohol intake in terms of liver disease for different populations. In the NHANES population, moderate alcohol intake is associated with increased ALT levels only in overweight and obese subjects, but not in normal weight persons, suggesting that alcohol exacerbates NAFLD (Ruhl CE. *Clin Gastroenterol Hepatol* 2005;12:1260). Prospective evaluations of alcohol intake and progression of NAFLD and other liver diseases are needed to better define safe alcohol intake in terms of liver disease risk. (10%)

C3a. Identify genetic markers for development of steatohepatitis and its complications. Linkage studies have identified several candidate genes associated with NAFLD, but larger studies using a greater number of patients and analyzing more polymorphisms are needed. (0%)

C3b. Develop screening programs for early detection and intervention with preventative or therapeutic regimens. Until accurate non-invasive markers for NAFLD and better information on means of treatment and prevention are available, screening programs cannot be initiated. (0%)

Figure 9. Estimated Progress on Fatty Liver Disease Research Goals, 2005 (Year 1)